REMARKS

This Supplemental Amendment and Response is being submitted in response to the Office Communication (Response to Amendment) mailed on January 27, 2005. In the Response to Amendment, the Examiner objects to the format of the Amendment to the claims filed on October 25, 2004. Specifically, the Examiner states that the applicants have not provided an accurate marked up version of the amended claims, *i.e.*, some of the language of the claims in the Amendment, which is indicated as the language of the claims as filed, is not present in the claims as filed.

Based on the telephone conversation with the Examiner on February 28, 2005, applicants understand that the Amendment and Response filed on October 25, 2004 have not been entered. Accordingly, applicants request entry of the present Supplementary Amendment and Response in place of the Amendment and Response filed on October 25, 2004.

Applicants respectfully note that, as follows from the Examiner's statements in the Response to Amendment mailed on January 27, 2005, the Examiner is mistaken in his belief as to the identity of the claims as filed in the present application. Applicants respectfully note that the present U.S. patent application is a National Phase (§371) of the PCT Application No. PCT/US00/19239, filed on July 14, 2000. Accordingly, the present application as filed should be the application transmitted by the International Bureau. Applicants further note that the claims as filed in the present U.S. application should be identical to the claims attached to the International Preliminary Examination Report entered by the Examining Authority (mailed on November 6, 2001; copy attached as Exhibit A). These claims are not identical to the claims originally filed in the PCT application but correspond to the claims as amended in the Response to Written Opinion filed on August 13, 2001.

However, applicants further note that the deleted language in claims 3, 4 and 13 as presented in the Amendment filed on October 25, 2004 did not correctly represent the language of these claims as filed in the present application. Specifically, the word "of" was missing after the word "catalysis" in line 2 of claim 3; the word "enzyme" was missing after the word "prothrombinase" in line 2 of claim 4; the phrase "is an exogenous prothrombinase" was

erroneously added before the phrase "factor Xa" in line 2 of claim 4; the word "catalyzed" was missing after the word "when" in line 5 of claim 13, and the phrase "the modified thrombin that is produced" was erroneously added before the phrase "a prothrombinase product assay" in line 7 of claim 13. Accordingly, applicants provide herein a Supplemental Amendment to the claims wherein the language of the claims as filed is properly reproduced.

I. Claim Status/Amendments. Claims 9 and 10 have been canceled, without prejudice or disclaimer. Claims 1-8 and 11-19 have been amended, without prejudice or disclaimer. By this Amendment, claims 1-8 and 11-20 are pending. Support for the amended claims is found throughout the specification, e.g., at page 3, lines 7-23; page 6, lines 17-18; page 7, lines 1-10; page 10, lines 26-30; page 11, lines, 16-30; page 13, lines 9-22; and original claims 1-20. Applicants note particularly that that the specification supports the term "prothrombin-converting enzyme" that is recited in amended claims 1, 4 and 13. The specification refers, e.g., to "prothrombinase" as "any substance which converts prothrombin to thrombin" (specification at page 6, lines 17-18). The specification furthers refers the terms "prothrombinase substrate" and prothrombinase product" as "the substrate and product involved in prothrombinase-mediated catalysis" (specification at page 7, lines 1-3). Example 1 further describes measuring the product producted by, among other reactions, a reaction of normal or actylated prothrombin, factor Xa, plus either PS:PC or platelets, and calcium chloride (specification at page 16, lines 13-15). These passages convey to one of ordinary skill in the art that when the application was filed Applicants had possession of a mixture comprising a "prothrombin-converting enzyme," as set forth in the claims. Ipsis verbis recitation of the term used in the claim is not required.

Each amendment to the claims is supported by the application as filed. Accordingly, by this Amendment, no new matter has been added to the application.

II. Claim Rejections. The claim rejections set forth in the Office Action are summarized and addressed as follows:

(i) Rejections Under 35 U.S.C. § 112, first paragraph (enablement). Claims 1-3 have been rejected as being directed to a method comprising "detecting the catalysis" of a

prothrombinase. In response, without conceding the validity of the rejections, claims 1-3 have been amended. The amended claims are directed to "a method for assaying activation state of platelets," comprising steps (a) and (b), as set forth in claim 1. The amendments to claims 1-3 are believed to address and overcome the basis of the rejections. Reconsideration of claims 1-3 and withdrawal of all rejections thereof under 35 U.S.C. § 112, first paragraph for lack of enablement is requested, accordingly.

(ii) *(i) Rejections Under 35 U.S.C. § 112, second paragraph.* Claims 1-12 have been rejected as allegedly indefinite for including the term "detecting." The Examiner's position is that it is not known what catalytic entity is to undergo or receive "detecting." In response, without conceding the validity of the rejections or the Examiner's position, the claims 1-8, 11 and 12 have been amended. Claims 9 and 10 have been canceled.

Claims 1-8, 11, and 12 are now directed to a method for assaying platelet activation state. The method comprises providing a mixture comprising platelets, a prothrombin-converting enzyme, and a substrate for the prothrombin-converting enzyme, and assaying the production of a product produced in the mixture, which product does not activate platelets (*see* amended claim 1). Each of claims 2-8, 11, and 12 depend either directly or indirectly from claim 1 and are therefore, likewise, directed to a method comprising providing a mixture comprising platelets, a prothrombin-converting enzyme, and a substrate for the prothrombin-converting enzyme, and assaying the production of a product produced in the mixture, which product does not activate platelets. The basis of the present rejection of remaining claims 1-8, 11, and 12 is therefore believed to have been addressed and overcome.

The Examiner has objected to the term "associated" in claim 1. In response, without conceding the validity of the Examiner's position, claim 1 has been amended. The phrase "a prothrombinase which is associated with the platelet" does not appear in the amended claim. The basis of the present rejection is believed to have been addressed and overcome.

The Examiner has objected to recitation of the phrase "modified prothrombinase substrate" that appeared in claims 1-3, 5-7, 13, 15, and 16. In response, without conceding the validity of the Examiner's position, the claims have been amended and are now directed, in

relevant part, simply to a "substrate." The basis of the present rejections is believed to have been addressed and overcome.

For all of the reasons set forth above, all rejections of pending claims 1-8, 11-13, 15, and 16 under 35 U.S.C. § 112, second paragraph are believed to have been addressed and overcome. Reconsideration of pending claims 1-8, 11-13, 15, and 16 and withdrawal of all rejections thereof for alleged indefiniteness is requested, accordingly.

(iii) Rejections Under 35 U.S.C. § 102. Claims 1-5, 9-11, 13, 15, 17, 19, and 20 have been rejected as allegedly anticipated by Szczeklik et al., *Blood* 80:2006-2011 (1992) ("Szczeklik et al."). The rejections are traversed on the grounds that Szczeklik et al. fail to disclose the claimed invention.

Szczeklik et al. does not anticipate the claimed method because Szczeklik fails to teach a method comprising converting a modified prothrombinase-converting enzyme substrate (e.g., modified prothrombin) to a product which does not activate platelets (e.g., modified thrombin) and assaying the presence of the product. The Examiner's basis for asserting lack of novelty is based in part on the assertion that Szczeklik et al. describe a method for assaying the activation state of a platelet by measuring thrombin generation. Office Action at page 4. (See also Szczeklik et al. at page 2006, col. 2 under "Study Design" ("We measured thrombin generation, both in vitro and ex vivo...," emphasis added.)) Thrombin is not a prothrombinase product that does not activate platelets, as required in the claims (see claim 1, "said product having the property that said product does not activate platelets").

Applicants point out that the specification at page 7, lines 7-25 defines the terms "modified prothrombin" and "modified thrombin." Modified prothrombin (a prothrombinase substrate) is prothrombin which has been altered (e.g., by chemical derivatization or genetic mutation) so that, when catalyzed by prothrombinase, a modified thrombin (a prothrombinase product) is produced. Modified thrombin is thrombin which has been altered so that it does not activate platelets. Thus, the invention advantageously provides an assay system which is not self-activating and is therefore more quantitative than current systems.

In making the rejection, the Examiner disregards the express definitions of "modified prothrombin" and "modified thrombin," as well as "prothrombinase substrate" (e.g., prothrombin) and "prothrombinase product" (e.g., thrombin) in the specification (page 7, lines 1-25). Nothing in the references suggests that the thrombin disclosed therein fails to activate platelets.

Indeed, the prothrombin and thrombin molecules described in the reference is not modified in the context of any definition. The reference merely describes that aspirin depresses thrombin formation in clotting blood and goes on to state, "It is suggested that aspirin exerts this effect by acetylating prothrombin and/or macromolecules of platelet membrane." (Szczeklik et al., Abstract, emphasis added). According to the reference, however, the mechanism by which aspirin acts is "unknown." Szczeklik et al. at page 2010, col. 1, line 25-26. Hence, there is no evidence that Szczeklik et al. react a modified prothrombin with prothrombinase. Nor, in any event, do Szczeklik et al. describe assaying for any prothrombinase product other than thrombin.

In view of the foregoing, Szczeklik et al. does not anticipate the claimed invention. Where a reference fails to teach an element of an invention, it cannot anticipate that invention. Reconsideration of pending claims 1-5, 10, 11, 13, 15, 17, and 19-20 and withdrawal of the rejection thereof under 102(b) is requested, accordingly.

(iv) Rejections Under 35 U.S.C. § 103. Claims 8 and 14 are rejected as allegedly obvious over Szczeklik et al. in view of Phizicky & Fields, 59 Microbiol. Rev. 94 (1995) ("Phizicky & Fields"). Claims 12, 14, and 18 are rejected as allegedly obvious over Szczeklik et al. in view of Mattler & Bang, Thromb. Haemost. 38:776 (1977) ("Mattler & Bang"). The rejections are respectfully traversed, as follows.

In making the obviousness rejections, the Examiner relies on Szczeklik et al. as the primary reference. Each of the rejected claims is directed to production and assay of a modified prothrombinase product which does not activate platelets. (See: Claim 1, base claim for claims 8 and 12; claim 13, base claim for claims 14 and 18.) As discussed above, Szczeklik et al. fails to disclose a method comprising converting a prothrombinase substrate to a modified prothrombinase product which does not activate platelets and assaying the presence of the

modified product. Moreover, Szczeklik et al. lacks any suggestion whatsoever to modify a prothrombinase substrate to yield a modified prothrombinase product that does not activate platelets and assay formation of the modified product. The claims are therefore not obvious over Szczeklik et al. The Examiner cites Phizicky & Fields merely for the proposition that it would have been obvious to use plasmon resonance to measure protein concentration. Office Action at page 6. Without conceding the Examiner's position, however, Phizicky & Fields cannot cure the defect in Szczeklik et al. because Phizicky & Fields fail to suggest production and assay of a modified prothrombinase product which does not activate platelets. Similarly, the Examiner cites Mattler & Bang merely for the proposition that it would have been obvious to use a chromogenic substrate in order to detect thrombin activity. Without conceding the Examiner's position, however, Mattler & Bang cannot cure the defect in Szczeklik et al. because Mattler & Bang fail to suggest production and assay of a modified prothrombinase product which does not activate platelets. Accordingly, neither Szczeklik et al. alone, nor Szczeklik et al. in combination with either Phizicky & Fields or Mattler & Bang suggests production and assay of a modified prothrombinase product which does not activate platelets. Accordingly, the obvious rejections should be withdrawn.

For the reasons set forth above, the claims are not obvious over Szczeklik et al. in view of Phizicky & Fields nor over Szczeklik et al. in view of Mattler & Bang. Reconsideration of claims 8, 12, 14, and 18 and withdrawal of the rejections thereof under rule 103(a) is requested accordingly.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 1-8 and 11-20 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. No fee is believed due with this submission. However, if the Examiner believes otherwise, he is

hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

By _____

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Irina E. Vainberg, Ph.D.
Registration No.: 48,008
Agent for Applicant(s)

DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (fax)